Iran J Public Health, Vol. 52, No.2, Feb 2023, pp.334-339

Original Article

Bone Metabolism Parameters in Azerbaijani Pre and Postmenopausal Women with Diabetes

Sain Sattar Safarova

Department of Internal Medicine, Azerbaijan Medical University, Baku, Azerbaijan

***Correspondence:** Email: sainsafarova@gmail.com

(Received 21 Mar 2022; accepted 19 Jun 2022)

Abstract

Background: This study aimed to determine the directionality of changes in serum bone remodeling markers and bone mineral density in the pre- and postmenopausal women with diabetes mellitus.

Methods: This study was carried out during the years 2016–2017 on the basis of Azerbaijan Medical University and included 142 pre- and postmenopausal women with type 1 and 2 diabetes mellitus (DM 1and DM2) were compared with 43 age-matched non-diabetics. The groups evaluated Ca^{2+}, PTH, CT, 25(OH)D levels, serum bone remodeling markers (ALP, P1NP, b-CTx), lumbar spine, proximal and femoral neck areas using DXA assessment.

Results: The results showed inconsistency observed between bone remodeling processes in women with diabetes. A negative correlation was observed between duration of diabetes and Lumbar T-scores (DM1: r = -0.568, *P* = 0.001; DM2: r = -0.267, *P* = 0.04). Lumbar T-scores was negatively correlated with b-CTx level (DM1: r = -0.452, *P* = 0.002; DM2: r = -0.357, *P* = 0.09). Postmenopausal groups with DM1 and DM2 were slightly higher b-CTx levels than premenopausal.

Conclusion: The patients with DM2 compared to DM1 had higher average BMD at all measured areas. Bone fragility is the result not so much of a decrease in BMD, but alterations in bone microstructure, as indicated by the disregulation of bone remodeling markers. This suggests that patients with diabetes are at a higher risk of bone turnover disorders compared to individuals without diabetes, which does not necessarily correlate with differences in BMD.

Keywords: Diabetes mellitus; Menopause; Bone

Introduction

Diabetes mellitus (DM) is a chronic metabolic disease that has an important impact on overall health (1, 2). Diabetes affects over 425 million adults worldwide and is projected to reach 629 million by 2045 (3). Until recent studies, the list of target organs affected by diabetes did not include bone tissue. The presence of this disease in anamnesis increases the probability of fractures, predisposing to a higher incidence of falls and decreasing bone mineral density (4). Postmenopausal bone tissue remodeling in the older age group of patients is induced or aggravated by DM, which leads to an increase in the incidence of hip fractures in type 1 DM (DM1) by 7 times,

and in patients with type 2 DM (DM2) up to 2.5 times compared with healthy individuals (5).
The aim of the study was to determine directionality of changes in serum bone remodeling markers and bone mineral density in the pre- and postmenopausal women with diabetes mellitus.

Materials and Methods

The study was carried out in the Department of Endocrinology of the Educational and Therapeutic Clinic at the Azerbaijan Medical University, Baku, Azerbaijan during the years 2016–2017.
The research was conducted according to the principles of the Helsinki Declaration and was approved by the local Health Research Ethics Committee of Medical University, protocol No. 02/14 dated 12.10.2016. After an explanation of the aim of the study, written informed consent from each participant was received.
This cross-sectional study included 57 women with DM1 and 85 women with DM2 in the pre- and post-menopause previously not diagnosed with osteoporosis. The age of surveyed women is from 40 to 68 yr (56.3 ± 0.9 and 57.6 ± 6.2 yr). Duration of diabetes: 17.08 ± 0.8 and 8.15 ± 4.6 yr, the mean value of HbA1c was 57 ± 0.2 and 58 ± 1.6 mmol/mol, neuropathy and retinopathy were detected in 42% and 88% of patients. The control group comprised of 43 women (55.4 ± 1.2 yr) without a history of diabetes.
Exclusion criteria: Women treated for osteoporosis or had a history of fracture, and patients with diseases of the endocrine system, liver, and kidneys of the non-diabetic nature, diabetic nephropathy of the 4-5 stage in the anamnesis.
Some subjects' characteristics were prospectively collected: BMI in kg / m2 (25.8 ± 0.3 and 30.2 ± 3.83 kg/m2) was calculated; menopausal status of surveyed women was assessed using the Cooperman index (duration of menopause averaged 13.4 ± 0.8 and 10.7± 0.6 yr).
Height and weight were measured by standardized techniques. BMI was expressed as weight per height squared (kg/m^2). Biochemistry panel, including HbA1c, total calcium (tCa), ionized calcium (Ca^{2+}), phosphate (P^{+}), creatinine, albumin, alkaline phosphatase (ALP), aminoterminal propeptide of procollagen type I (PINP), C-terminal telopeptide of type I collagen (beta-CTx) in serum, was measured using on an automatic electro-chemiluminescence analyzer (COBAS C, Roche Diagnostics GmbH Mannheim, Germany). Glomerular filtration rate (GFR) was calculated by CKD-EPI equation: (=141 x min (SCr(mg/dl)/k,1)a x max (SCr/k,1)-1,209 x 0.993 age (x1.018 if female) (in ml/min/1,73 m^2). Commercially available human ELISA assays of insulin, parathyroid hormone (PTH), calcitonin (CT) and vitamin D (25 (OH) D) were performed according to manufacturer's instructions. Insulin sensitivity was assessed by homeostasis model assessment of insulin resistance (HOMA-IR) using the following equation: (fasting insulin (mIU/l) × fasting glucose (mg/dl)) / 405.
All subjects underwent DXA on a densitometer (DXA HOLOGIC, Discovery QDR 4500A, USA) T-score of the lumbar spine (L1-L4), proximal (Prox) and femoral neck (FN) areas. WHO criteria for diagnosis of osteoporosis by BMD (T-score ≤ 2.5SD), osteopenia (T-score from -1 to -2.5 SD), and normal (T-score > -1).
The statistical analysis was carried out using STATISTICA 10 program. Data were presented as mean (M) and confidence interval (95% CI) unless specified otherwise. Statistical analysis was done using unpaired parametric data analyzed by Mann—Whitney U test. Spearman's rank correlation was calculated to assess the power of connection between the parameters. A value of $P<0.05$ was considered statistically significant.

Results

Overall, 142 pre- and postmenopausal women with diabetes as a case group and 43 women, without diabetes mellitus, as a control group was recruited in this case-control study. In groups with DM1 and DM2, the average levels of tCa tend to be lower than control group, however, they corresponded to the age reference range,

with tendency towards lower in postmenopausal women. Ca^{2+} levels in the DM1 and DM2 groups were significantly lower than in the control group; the maximum decrease in Ca^{2+} serum levels was observed in the postmenopausal subgroup of patients with DM1 (P =0.024). In the control group, the mean serum P^{+} levels in postmenopausal women were significantly lower than in patients with DM1 and DM2 (P=0.013; P=0.029) (Table 1).

Table 1: Clinical parameters in the groups

Group	***T1DM, n=57***		***T2DM, n=85***		***Non-DM Controls, n=43***	
Variables	Premenop., N=12	Postmenop., N=45	Premenop., N=14	Postmenop., N=71	Premenop., N=15	Postmenop., N=28
Age, years	56.3 (54.4-57.3)		57.6 (57.3-59.5)		55.4 (54.2-57.7)	
BMI. kg / m ^{2}	25.8 (25.6- 26.5)		30.2 (29.4-30.6)		28.7 (27.9-29.5)	
Duration of DM, (years)	17.08 (15.4-18.9)		8.15 (7.2-8.8)		-	
HOMA-IR	-		2,8±2,2 [a2]		1,7 ± 1,5	
HbA1c, mmol /mol	57 (54-62)		58 (55-62)		30 (28-31)	
Menopause, (years)	-	14,2±0,71 (12,7 15,6)	-	12,1±0,62 (10,9 13,4)	-	11,3±1,11 (9,05 13,6)
GFR, ml/min/1,73 m^2	104,3±6,49 (90,05-118,6)	79,4±1,95 (75,4 83,3)	101,2±4,09 (92,3-110,1)	83,0±1,80 (79,4-86,5)	100,7±3,21 (93,7-107,5)	84,9±2,49 (79,8-90,04)
tCa, mg/dL	9.4±0.08 (9.2-9.5)		9.4±0.05 (9.3-9.5)		9.4±0.07 (9.2-9.5)	
	9.4±0.19	9.3±0.08	9.6±0.09	9.4±0.06	9.5±0.16	9.3±0.08
Ca^{2+}, mmol/L	1.06±0.01 (1.03-1.08) [a]		1.06±0.01 (1.03-1.09) [a]		1.1±0.01 (1.07-1.12)	
	1.09±0.02	1.05±0.01 [a]	1.07±0.04	1.06±0.02 [a]	1.12±0.02	1.09±0.01
P, mg/dL	5.3±0.14 (5.1-5.6)		4.9±0.10 (4.7-5.1)		5.04±0.13 (4.7-5.3)	
	5.6±0.34	5.3±0.15 [a]	5.1±0.20	4.9±0.12	5.3±0.21	4.8±0.14
PTH, pg/dL	53.99±2.21 (49.5-58.48) [a]		50.18±1.71 (46.74-53.61)		48.3±3.13 (41.8-54.79)	
	42.49±6.24	56.29±2.16 [b]	44.41±2.54	52.31±1.95 [b]	42.15±6.69	50.83±3.41
25(OH)D, ng/mL	21.85±1.6 (18.59-25.1) [a]		24.11±1.31 (21.48-26.73)		27.56±2.48 (22.45-32.66)	
	25.34±4.06	20.68±1.64	29.35±5.18	23.17±1.23	29.71±5.06	26.48±2.81
CT, pg/mL	12.54±1.43 (9.61-15.47) [a2]		10.65±0.88 (8.88-12.43) [a]		6.88±0.93 (4.94-8.83)	
	6.1±2.09	14.35±1.57 [ab]	4.9±0.87	11.83±0.94 [ab2]	3.36±1.65	8.43±0.92 [a2]
ALP, IU/L	112.5±5.08 (102.35-122.71)		121.0±3.78 (113.5-128.6)		115.6±6.67 (102.1-129.03)	
	109.5±10.62	113.3±5.83	112.5±7.95	122.7±4.24	110.4±9.16	118.3±9.06
PINP, ng/mL	36.69±2.03 (32.61-40.77) [a4]		42.03±1.32 (39.41-44.65) [a]		49.72±3.14 (43.39-56.03)	
	43.59±7.12	34.85±1.71 [a2]	47.1±4.32	41.03±1.31 [ab]	53.55±5.44	47.67±3.85
b-CTx, ng/mL	0.563±0.04 (0.477-0.650)		0.511±0.02 (0.460-0.563)		0.483±0.03 (0.420-0.547)	
	0.510±0.09	0.578±0.04	0.457±0.06	0.522±0.02	0.437±0.05	0.508±0.03
T-score (L1-L4)	-2.48±0.2 (-2.8; -2.1) [a3]		-1.26±0.16 (-1.5; -0.9)		-1.37±0.26 (-1.9; -0.8)	
	-2.01±0.39 [a]	-2.61±0.23 [ab2]	-0.80±0.35	-1.35±0.18	-0.81±0.3	-1.67±0.36
T-score (Prox)	-1.87±0.18 (-2.2; -1.5) [a4]		-1.03±0.16 (-1.3; -0.7)		-0.69±0.21 (-1.1; -0.2)	
	-1.28±0.34	-1.99±0.2 [a3b]	-0.80±0.18	-1.07±0.19	-0.34±0.28	-0.86±0.27
T-score (FN)	-2.01±0.19 [a3] (-2.4; -1.6)		-1.27±0.15 (-1.5; -0.9) [a]		-0.83±0.23 (-1.3; -0.3)	
	-1.52±0.41	-2.11±0.22 [a2]	-0.94±0.28	-1.32±0.17 [a]	-0.53±0.38	-0.99±0.29

Legend: [a] - P<0.05; [a2] - P<0.01; [a3] - P<0.005; [a4] - P<0.001 compared with the control group data;
[b] - P<0.05; [b2] - P<0.01 compared with subgroup premenopausal patients

In the control group, serum PTH levels was higher in comparison with the DM1 group and in both groups increase in postmenopause. In women with longer duration of diabetes, serum level of PTH was significantly different from that in women with diabetes duration less than 10 years (P=0.034; P=0.047). There was significant negative correlation between serum PTH levels and P1NP (r=-0.532, P=0.001) and also a positive correlation between serum PTH levels and bone resorption marker b-CTx (r=0.413, P=0.002). In patients with DM1 and DM2, the level of vitamin D decreases below the lower reference range, compared with the control group (P<0.05), with a tendency to decrease in postmenopausal women in both groups. In addition, patients in the case group had correlation of Ca^{2+} level and vitamin D with serum levels of PTH (r=-0.378, P=0.01 and r=-0.461, P=0.001). In postmenopausal women of the control group, the level of serum CT was significantly lower than in diabetic patients.

Data analysis in research is an indicate increase in the serum level of PTH and CT against reduction in the concentration of calcium ions, which demonstrate disorder of bone remodeling and relationship between an unbalanced serum calcium-regulating hormones level and diabetes mellitus. It should be noted that with an increase in the duration of the disease and in the stage of decompensation, the severity of these changes increases.

Patients with DM1 and DM2 (35.5% and 18.3%) shows decreasing trend for formation marker PINP levels (P<0.05), and an increase in the marker of bone resorption b-CTx in 16.6% and 5.8% of patients compared with the control group. In the postmenopausal subgroup of patients with DM1 and DM2, the amount of b-CTx was slightly higher than in premenopausal women. However, it did not elevate beyond according to the age reference ranges. Some women with DM (20%) showed a decrease in the bone formation marker PINP, which did not affect bone resorption.

The P1NP level was negatively correlated with HbA1c (DM1: r=-0.328, P=0.03; DM2: r=-0.301, P=0.02). Positive correlation was found between the duration of DM and serum level of b-CTx (DM1: r=0.349, P=0.08; DM2: r=0.214; P=0.04). A significant correlation between the serum levels of PTH and CTX, found in the group of patients with DM1 and DM2, was also confirmed (r=0.413, P=0.002 and r=0.507, P=0.001).

In DM, prevalence of low spinal (L1-L4) BMD in women was 75%, in the proximal femur and femoral neck -39%. In 83 females out of 142 patients with DM, only T-score of the lumbar spine changes were found, in 32 females only in the T-score of femoral neck. In at least 24 patients, a combination of changes in both zones was determined using DXA. At the same time, a part of patients (n=115) who had changes in only one measured area, the risk of an erroneous diagnosis increases significantly. In the control group, the number of cases of spine osteoporosis (L1-L4) was 14%, in the proximal femur and femoral neck -2.3% and 7%. Vertebral osteopenia was found in 23% of women. Osteopenia in the proximal femur and femoral neck of the control group patients were found in 26%, and 28% of cases. A negative correlation was observed between T-score of L1-L4 area and duration of diabetes (DM1: r=-0.568, P=0.001; DM2: r=-0.267, P=0.04). In postmenopausal women with diabetes, a decrease in BMD correlate with an increase in the duration of the disease, with concomitant age-related changes (DM1: r=-0.515, P=0.01 and DM2: r=-0.416, P=0.04). A statistically significant correlation was observed between the T-score of L1-L4 area and b-CTx level (DM1: r=-0.452, P=0.002; DM2: r=-0.357; P=0.09).

Discussion

If in general, the processes of bone formation and resorption are closely related, and formation markers and resorption markers tend to change in a coordinated manner, then in patients with diabetes observed dissociation of these processes,

while formation markers are reduced, and found no changes in bone resorption markers. Data from a number of researchers also indicate a moderate decrease in bone formation markers in diabetes, accompanied by normal levels of bone resorption markers in most studies (6, 7). Markers of bone metabolism indicate very specific changes in bone remodeling processes associated with a disruption in the metabolism of carbohydrates in diabetes, when the formation markers are reduced, while the resorption markers do not change, apparently due to hyperglycemia-induced inhibition of osteoblastic function (8). It is possible that blood glucose concentration changes may affect the circulating concentrations of these bone metabolic markers (7, 9), which can clinically increase the bone fragility in patients with diabetes.

The study showed that in most patients, altered bone metabolism is associated with inhibition of bone formation and, to a lesser extent, with bone resorption. Therefore, premenopausal women with type 1 diabetes, according to the results of measurement of biochemical markers of bone remodeling, the inhibition of bone formation processes were determined and the processes of bone tissue resorption were enhanced. In premenopausal women with DM2, a less pronounced increase in the activity of bone resorption biochemical marker was determined than in DM1, while the formation marker did not differ from the values of the control group. This indicates the different directions of the pathogenetic mechanisms of the development of diabetic osteopathy in the early stages of type 1 and type 2 diabetes. In postmenopausal patients with DM1 and DM2, the mean b-CTx levels was slightly higher than in premenopausal women. In addition, correlation was found between duration of DM with the level of b-CTx and the T-score measured in the lumbar spine area. Both bone metabolism markers and DXA are independent factors indicative of changes in bone tissue, which can be of great importance for early diagnosis and evaluation of the effectiveness of the therapy (8, 10).

Conclusion

The patients with DM2 compared to DM1 had higher average BMD at all measured areas. Bone fragility is the result not so much of a decrease in BMD, but alterations in bone microstructure, as indicated by dysregulation of bone remodeling markers. Patients with both type of diabetes are at an increased risk of bone turnover disorders compared to individuals without diabetes, which does not necessarily correlate with differences in BMD.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Acknowledgements

This review did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Conflict of interest

The authors declare that there is no conflict of interests.

References

1. Pramojanee SN, Phimphilai M, Chattipakorn N, Chattipakorn SC (2014). Possible roles of insulin signaling in osteoblasts. *Endocrine Research*, 39 (4): 144-151.
2. Vestergaard P, Rejnmark L, Mosekilde L (2009). Diabetes and its complications and their relationship with risk of fractures in type 1 and 2 diabetes. *Calcif Tissue Int*, 84 (1): 45-55.
3. International Diabetes Federation, IDF Diabetes Atlas, International Diabetes Federation, Brussels, Belgium, 8th edition (2017). http://www.diabetesatlas.org

4. Farr JN, Khosla S (2016). Determinants of bone strength and quality in diabetes mellitus in humans. *Bone*, 82: 28-34.
5. Khan TS, Fraser LA (2015). Type 1 diabetes and osteoporosis: from molecular pathways to bone phenotype. *J Osteoporos,* 2015: 174186.
6. Al-Hariri M (2016). Sweet bones: the pathogenesis of bone alteration in diabetes. *J Diabetes Res*, 2016: 6969040.
7. Safarova S (2018). Evaluation of bone turnover in patients with type 1 diabetes mellitus. *J Endocrinol Metab*, 8 (1): 2-5.
8. Ghodsi M, Larijani B, Keshtkar AA, et al (2016). Mechanisms involved in altered bone metabolism in diabetes: a narrative review. *J Diabetes Metab Disord*, 15: 52.
9. Juliana S Cunha, Vanessa M Ferreira, Edgar Maquigussa, et al (2014). Effects of high glucose and high insulin concentrations on osteoblast function in vitro. *Cell Tissue Res*, 358 (1): 249-256.
10. Starup-Linde J, Vestergaard P (2016). Biochemical bone turnover markers in diabetes mellitus-a systematic review. *Bone*, 82: 69-78.